PHÆOCHROMOCYTOMA

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The successful diagnosis and removal of phæochromocytomata have been reported with increasing frequency during the past few years, and it is probable that many cases have been missed in the past. At this hospital, six tumours have been removed since 1948, while none was recognized either at operation or post mortem during the preceding twenty years.

This paper is based on five cases, three of them not previously described and two reported by Barnett *et al.* (1950). It is concerned especially with the clinical diagnosis and its confirmation by such methods as the biological assay of adrenaline and noradrenaline in the urine, the use of so-called adrenolytic drugs, and the estimation of skin blood flow. We also report assays of the urine and of the tumours in two cases not under our care.

Case Reports

Case 1. W.H., a man, aged 38, was well until 1946, when he developed increasing lassitude and anorexia and was found to have a B.P. of 180/110. Subsequently, he developed attacks of pallor, sweating, "goose-flesh," vomiting, and breathlessness. He was admitted to Chase Farm Hospital on 20/7/48 in a particularly severe attack, and was diagnosed as having a phæochromocytoma by Dr. T. Simpson. There was profuse sweating and pallor, a B.P. of 200/140, bilateral papillœdema with retinal exudates and hæmorrhages, cardiac enlargement, pulsus alternans, gallop rhythm, and a mass palpable in the right loin.

A phæochromocytoma was removed at St. Mary's Hospital on 23/9/48; he has remained symptom-free since with resolution of the retinal changes, but the blood pressure which was 160/120 until 10 months after the operation had risen to 230/130 four years afterwards.

Case 2. B.H., a man, aged 31, had attacks of pallor and bradycardia as a boy of eleven which had led to the discovery of a left bundle branch block with short P–R interval (Case 7 of Wolff, Parkinson, and White, 1930). These attacks subsided, but at the age of twenty-three he began to get attacks of epigastric discomfort, followed by slow, forceful palpitation, pallor, and sometimes throbbing headache, nausea, vomiting, and dyspnœa. His blood pressure between attacks varied from 120/86 to 170/110 and always rose during attacks, the highest recorded being 254/154. They were also marked by sweating, shivering, and slight bradycardia.

A phæochromocytoma was removed on 12/11/49. He has been symptom-free since, his blood pressure on 6/6/52 being 135/80.

Case 3. M.J., a women, aged 66, who had attacks of palpitation for 2 years, was admitted to hospital after three attacks of severe dyspnœa with copious expectoration, sweating, and vomiting. The skin was found to be pale, cold, and sweating; the blood pressure varied from 150/90 to 270/180; marked enlargement of the left ventricle was present, with a presystolic gallop rhythm, and there were retinal hæmorrhages and soft white exudates, but no papillœdema. Rises in the very labile blood pressure were associated with increased pallor, sweating, vomiting and usually tachycardia, but no sharply defined paroxysms were observed.

Removal of a phæochromocytoma from above the right kidney on 30/10/51 was followed by a disappearance of all symptoms. Eleven months later the blood pressure was 165/100.

Case 4. E.G., a women, aged 40, with neurofibromatosis, was admitted to hospital having had attacks

of palpitation for 5 years accompanied by headache, dyspnœa, sweating, and often preceded by vomiting. She had been increasingly breathless on exertion for 9 months. The systolic pressure between attacks varied from 230 to 200 mm. Hg and the diastolic from 150 to 120 mm. Hg. Attacks, lasting 5–10 minutes, of extreme pallor, sweating, dyspnœa, and tachycardia were accompanied by a rise of pressure to over 300/200 mm. There was presystolic gallop rhythm but no cardiac enlargement. Papillœdema, retinal hæmorrhages, and exudates were present.

Removal of a phæochromocytoma on 10/12/51 was followed by a disappearance of symptoms and a gradual regression of the retinal changes, but the blood pressure, after a temporary fall, was 240/140 seven weeks after the operation.

Case 5. D.K., aged 33, recently qualified as a doctor, had been troubled for 4 weeks by attacks in which he developed a sense of constriction in the throat, regular, forceful, but not rapid palpitation, and a throbbing frontal headache with occasional vomiting. He and his friends observed a swelling in the neck during the attacks which they attributed to enlargement of the thyroid gland. Blood pressure varied from 120/60 to 140/80 between attacks and rose to a maximum of 214 mm. Hg systolic and 105 diastolic during attacks, which were accompanied by slight pallor, sweating, and bradycardia, and by an increase of 3–5 cm. in the neck circumference due to swelling of the thyroid gland.

A phæochromocytoma was removed on 20/12/51. He has been symptom-free since and his blood pressure was 120/65 nine months later.

The urinary excretion and tumour content of pressor amines was also estimated in two other cases not seen by us who had phæochromocytomata successfully removed. These results are given in Tables III and IV under Case F (by kind permission of Dr. F. T. G. Prunty of St. Thomas's Hospital, London) and Case G (by kind permission of Dr. C. M. Seward and Dr. G. M. Colson of the Royal Devon and Exeter Hospital).

Diagnosis

Although reliance on pharmacological tests to confirm the diagnosis of phæochromocytomata is likely to increase, the recognition of certain combinations of symptoms will always be essential in suggesting the possibility of the condition. The majority of these symptoms have been adequately described (Mackeith, 1944; Smithwick *et al.*, 1950) and need only brief mention here.

All our patients had symptoms that should suggest the diagnosis. Attacks of palpitation were a prominent feature in four of them and were always remarkable for their forcefulness; in two (3 and 4) they were rapid, and in two (2 and 5) slow. We would emphasize that palpitation, associated with bradycardia, is a fairly common feature of this condition. The ratio of excreted noradrenaline to adrenaline was high in Cases 3 and 4, who showed tachycardia, whereas it was relatively low in Case 5, who had bradycardia in his attacks. High noradrenaline output should therefore not necessarily be inferred in patients with this lesion who show bradycardia, despite the findings of Barcroft, Konzett, and Swan (1951), who usually noted bradycardia during infusions of small amounts of noradrenaline. One of us (W.S.P.) has observed tachycardia during infusions of larger quantities of noradrenaline in two patients.

The onset of palpitation was not always clearly defined. It usually lasted 5–15 minutes, but might last several hours. In all, the attacks ended by gradual reduction in the vigour of the pulsations, and tachycardia, if present, subsided gradually. Severe and throbbing headache sometimes occurred with the palpitation, and was often associated with vomiting. Pallor, sweating, and some degree of breathlessness during the more severe attacks were usually noticed by the patients. " Goose-flesh " (Cases 1 and 5) and retrosternal pain (Cases 2 and 4) were each reported by two patients, and the attacks occurred at night in four (Cases 2, 3, 4, and 5). Sensations of fear were volunteered by only one (Case 1).

The appearance of the patients during an attack was striking. Beads of sweat were usually visible on a uniformly pale skin, which was cold to the touch, and the forcibly beating heart shook the whole chest. The observation by relatives and friends of such objective changes during an attack may be helpful since the symptoms are often thought to be due to a nervous tachycardia. The wife of one patient (Case 2) strongly rebutted such a diagnosis on the grounds that she was often wakened before her husband by the shaking of the bed during his attacks at night.

The hypertension in two cases (2 and 5) was intermittent with normal pressure between attacks. In the other three (1, 3, and 4) the pressure never fell to normal levels, but the term "chronic (or sustained) hypertension" (Green, 1946; Swan, 1951) seems inappropriate in view of the marked variability of the pressures. Although from time to time cases of phæochromocytoma are reported with little variation in the blood pressure (Lumb, 1951), we have not seen a case in which the hypertension showed the degree of stability observed in most patients in hospital with essential hypertension.

Left ventricular failure is a well-recognized danger for such patients, and occurred in Case 3 with typical cardiac asthma. Together with retrosternal pain, it is, perhaps, responsible for the occasional mistaken diagnosis of myocardial infarction in phæochromocytoma.

Certain less-known features observed in our patients deserve mention. In two (Cases 2 and 5) attacks were precipitated by straining at stool; we have been unable to find any previous account of this. One (Case 2) thought attacks were associated with lying on the right side, and precipitation by exertion was noted in Cases 2 and 5, although the attacks were no more severe than those occurring at rest.

Enlargement of the thyroid gland during attacks has been recorded in this condition (Strombeck and Hedberg, 1939; Bauer and Belt, 1947). It was observed previously in this hospital that infusions of noradrenaline repeatedly produced such a swelling in one normal subject (Barnett *et al.*, 1950). No vascular bruit was heard over the thyroid in such incidents in our patient (Case 5), but it would seem likely from the rapid development and subsidence of the swelling that it is due to vascular engorgement. Its occurrence is so distinctive that its value in diagnosis can well be stressed.

Auriculo-ventricular dissociation (ventricular rate 50) was detected in Case 5 during attacks by noting a variation in the intensity of the first heart sound and was confirmed by electrocardiography. It has been described in this condition (Burgess *et al.*, 1936) and reproduced experimentally by noradrenaline infusion by Barnett *et al.* (1950), who attributed it to vagal stimulation in response to the rise of blood pressure.

Neurofibromatosis (Case 4) was found in 9 of the 152 cases reviewed by Mackeith (1944). The association with the Wolff-Parkinson-White syndrome found in Case 2 has not, to our knowledge, been previously reported and is probably fortuitous.

Transient blurring of vision during attacks (Case 2), lasting for a number of hours, is an unusual symptom. We have no evidence as to its cause. It is recorded also by Crowther (1951).

Two of our patients (Cases 1 and 4) had papillœdema and, with one other (Case 3), showed retinal hæmorrhages and soft exudates. Two, and possibly three, therefore, had hypertension in the malignant phase, as judged by the fundi. In all three the renal functions tested were normal; the urine of two (Cases 3 and 4) contained albumin and granular casts, but that of Case 1 showed neither albumin nor casts. Arteriolar fibrinoid necroses were not found in the adrenals of any of our cases, nor in a renal biopsy taken from Case 1. In a review of 50 published cases, Green (1946) was able to find only 4 instances of malignant hypertension, but clinical criteria alone were mentioned for this diagnosis. Platt and Davson (1950) report a case with bilateral phæochromocytomata, whose kidneys showed the "naked eye and microscopic characteristics of malignant nephrosclerosis."

Two patients showed fever and leucocytosis, which are not uncommon in this condition; thus in Case 1 the temperature rose on occasions to 102° F and a blood count showed 14,000 W.B.C. per c.mm. with 62 per cent neutrophil polymorphs; the fever was less marked in Case 3 (99°–100° F), and the blood contained 15,000 W.B.C. per c.mm. with 75 per cent neutrophil polymorphs. We have been unable to correlate these signs with hæmorrhage into the tumour.

The duration of the paroxysms was between 5 and 30 minutes in the cases with intermittent hypertension (2 and 5), as it was in the early stage of Case 1; Case 4 throughout showed paroxysms of a similar length. The attacks in the latter stages of Case 1 were too ill-defined for estimation of their duration; in Case 3 they continued for as long as six hours.

Localization of the Tumour

All five patients in this series had right suprarenal tumours. Evidence as to localization was forthcoming in all except one (Case 4); a palpable mass in the abdomen in Case 1 was confirmed as a suprarenal tumour by perirenal air insufflation; increasing tenderness in the upper abdomen was on the same side as a radiological soft-tissue shadow in Case 5, and a soft-tissue shadow alone in Case 2 was sufficient to lead to the exploration of the correct suprarenal; in Case 3, the low position (both clinically and radiologically) of the kidney was the sole (but correct) indication.

Thus there was direct evidence of a tumour of the suprarenal gland in three cases (1, 2, and 5). In the other two perirenal air insufflation was considered but rejected because of the risks, not only of air embolism (Blackwood, 1951), but also of precipitating severe paroxysms of hypertension (Mackeith, 1944) in patients showing left ventricular failure and malignant hypertension. In view of the high proportion of right-sided tumours in reported cases (Strombeck and Hedberg, 1939; Smithwick *et al.*, 1950), the safest procedure in these two was considered to be exploration of, first, the right suprarenal and then, if necessary, the left. In both instances the tumour was found at the first operation.

Localization by unilateral abdominal compression, with the induction of a paroxysm thereby, was not successful in our patients.

Special Diagnostic Procedures

Maximal Heat Elimination from the Hand. The heat elimination from the hand, made maximal by rapidly heating the body, is a measure of the rate of blood flow through the hand after release of vasomotor tone from its vessels (Pickering, 1936). It was measured by following the temperature changes of water in a calorimeter in which the hand is immersed as described by Barnett *et al.* (1950). In four of the patients it was abnormally low, but in Case 5 it was normal (Table I). Two of the patients had hypertensive attacks during this test, with a further fall in heat elimination (Cases 2 and 4). Following operation the maximal heat elimination rose to the normal level (above 60 calories per 100 ml. of hand per min.) even in the patients in whom hypertension persisted (Cases 1 and 4).

TABLE I

Maximal Heat Elimination

Case	Calories per 100 ml. of hand per min.		B.P. during test, mm. Hg	
	Before operation	After operation	Before operation	After operation
1 W.H.	35	90	160/115	200/140
2 B.H.	24	76	130/90	122/82
3 M.J.	37	80	220/120	180/85
4 E.G.	34	86	190/140	150/90
5 D.K.	93	116	130/86	116/74

The low values for heat elimination obtained before operation in all our patients, except Case 5, support the view that circulating vasoconstrictors are usually present in this condition, particularly since the values rose to normal after operation. There is not necessarily a raised blood pressure at the time of a test which gives a low value, perhaps indicating that the circulating amines are sufficient to constrict the skin vessels without causing a general rise of blood pressure. The maintenance of normal pressures may be due to dilator reflexes, which do not affect the skin vessels. It is not known whether it is possible to infuse noradrenaline or adrenaline at a rate sufficient to constrict the hand blood vessels without causing a rise of blood pressure. The precipitous fall in blood pressure, which occurs in most patients immediately after the tumour is removed, suggests that depressor mechanisms have been called into play by the circulating pressor amines, but there is as yet no evidence as to whether the depressor mechanisms are humoral or nervous.

Blacket *et al.* (1950) observed a similar fall in rabbits' blood pressure after stopping infusions of noradrenaline, and suggested a humoral mechanism on indirect evidence.

Case 5 had a normal heat elimination, even during a minor attack. This test is therefore fallible, but remains a simple and useful one.

Pharmacological Diagnosis. Some of these methods of diagnosis have recently been reviewed (Entwisle *et al.*, 1951; Evans *et al.*, 1951), and consist in the use of so-called antagonistic drugs, like piperoxane (Goldenberg *et al.*, 1947), or " stimulating drugs," which precipitate typical hypertensive attacks, like histamine (Roth and Kvale, 1945). Our procedure in using the antagonistic drugs was to set up an intravenous infusion of saline and to inject the drugs into the tubing. The effect of a control saline injection was compared with that of the antagonistic drug. A maximum of 20 mg. of piperoxane was given in one minute; sometimes headache, nausea, or substernal or abdominal pain stopped the injection. The results of such injections are shown in Table II.

TABLE II

THE EFFECTS OF INFUSIONS OF PIPEROXANE

Case	Dose (mg.)	B.P. mm. Hg	
		Before injection (mean)	After injection (maximal effect)
1 W.H.	15	185/125	225/130
3 M.J.	20	200/120	170/70
4 E.G.	8	224/140	250/160

Experience here with piperoxane has been discouraging, since the test was negative in Cases 1 and 4, though positive in Case 3. Goldenberg and Aranow (1950) suggest that the negative results in proven cases may be due to a secondary hypertension. This is supported by the persistence of the hypertension after removal of the tumours in these two cases. False negative results have been reported by Tulloh (1952) and false positives in uræmic hypertensives (Emlett *et al.*, 1951). The side effects of this drug are frequently unpleasant, and the use of " regitin " (C7337) has been recommended, since it is said to give a more definite and prolonged fall in pressure, with few side effects (Emlett *et al.*, 1951). It was injected in a dose of 0·08 mg. per Kg. during one minute. In Case 3 it was used before operation for diagnosis, the pressure falling from 230/130 to 160/70 within three minutes. The effect, although less, was still present two hours after injection, when the pressure was 190/105. It was also used in Case 4 to control the rapid rise of pressure during operation, and caused a fall from 260/160 to 170/105 within one minute.

These drugs are, of course, useless for diagnosis in cases where the blood pressure is usually normal and only raised for short episodes. The use of drugs like histamine, which precipitate attacks, is clearly to be avoided if possible, as they may not be without risk, and both false negative and positive results have been reported (Evans *et al.*, 1951). They were not used in these cases.

Pressor Substances in Blood, Urine, and Tumour. The original observation that an adrenaline-like substance was present in the blood of a patient with this condition was made by Beer *et al.* (1937). Owing to the low concentrations usually present and the non-specificity of many methods, this assay is difficult by any means. A firm basis for the diagnosis was claimed by Engel and Euler (1950) by estimation of the daily urinary excretion of adrenaline and noradrenaline. They reported cases where the excretion was greatly raised, and further reports appeared by Euler (1951) and Goldenberg (1951). These findings have been confirmed (Table III).

Method—Urines. The method of estimation used here was based on that of Euler and Hellner (1951). The urine was not hydrolysed with HCl, so that only the free amine in the urine was estimated. The amines were extracted from part of a 24-hour specimen by selective adsorption on alumina. They were assayed biologically using the blood pressure response (Hg manometer) of the anæsthetized rat (nembutal 4–5 mg.

per 100 g. intraperitoneally). The total pressor amines were estimated by matching with known solutions of adrenaline and noradrenaline. The ratio of noradrenaline to adrenaline in the mixture was measured by using dihydroergotamine which reverses the action of adrenaline, but merely reduces the pressor action of noradrenaline. A mixture of the amines then gives a biphasic response with an initial fall due to adrenaline, followed by a rise due to noradrenaline. The response given by the urine extract was matched with the appropriate mixture of noradrenaline and adrenaline.

TABLE III

TOTAL 24-HOUR URINARY EXCRETION OF PRESSOR AMINES (μG.)

Case	Before operation		After operation (total)
	Total	Ratio (noradrenaline/adrenaline)	
3	4375	3·0	40
4	500	4·0	70
5	412	1·5	45
F	1082	9·0	25
G	600*	0·5	—

* Urine collected for 14 hours only.

The maximum daily excretion found here in 28 patients with hypertension not due to phæochromocytomata was 70 μg. noradrenaline and adrenaline as the free amines. The daily excretion in the proved cases here reported was always more than five times this value. As might be expected, the excretion in phæochromocytomata is partly paroxysmal; thus in Case 4, 100 ml. of urine collected in the hour following a severe attack contained 500 μg. of pressor amine, as compared with the same amount excreted during 24 hours when only slight attacks were experienced. The case which best demonstrates the value of the urinary assay is Case 5, who had only three attacks of 5 minutes duration in one 24-hour period, yet excreted six times the normal amount. The amine release from the tumours, while partly paroxysmal, is probably continuous in some cases, as is suggested by the low maximal heat eliminations discussed previously. Patients with great differences in the severity of their symptoms and signs may have, on occasion, the same level of urinary excretion. Case 4, with severe attacks, had a similar 24-hour urinary excretion to Case 5, with slight attacks (Table III). The level of excretion is directly related, however, to the severity of the attacks during the period of urine collection, and a patient with severe, frequent attacks always had a higher excretion than one with mild, intermittent attacks (see discussion of Case 4, previously). There is therefore no evidence that individual variation in response to the same amount of circulating amine could account for the difference in severity of the symptoms. It has been claimed by Shapiro *et al.* (1951) that a patient with a phæochromocytoma was less sensitive to injected adrenaline than normal subjects. It must be pointed out that it is not known if the level of urinary excretion is directly or uniformly related to the blood level of these amines. Little is known about excretion of large amounts of adrenaline and noradrenaline, but Euler and Luft (1951) found that only 1 per cent of noradrenaline infused in small amounts (10–20 μg. per minute) was excreted in the urine. In Case 3, who had severe attacks and a very high urinary excretion, presumably a much greater percentage of amine was excreted. After operation the excretion returned to normal in all cases, and remained so in Case 4 despite the subsequent rise of blood pressure. The excretion in Case 1 was not measured before operation, but 3½ years after operation, when his blood pressure was 200/140, his excretion was normal.

Excretion in the urine is not the only way in which adrenaline and noradrenaline are removed from the circulation. They also occur in the urine as inactive ethereal sulphates and glucuronides. We have not investigated the possibility of marked individual variation in this mode of inactivation. Oxidation by amine oxidase is another conceivable means of removal (Burn, 1952).

Method—Tumours. Part of the tumour was taken into 10 ml. N/10 HCl per g. of wet tissue and ground up. The rest was used for sections. All showed the typical naked-eye and microscopic features of phæochromocytomata. The amine content of the tumours was assayed by the same method as for urine, though it was found possible to use dilutions of the neutralized crude extracts in the rat without depressor effects.

TABLE IV

PRESSOR AMINE CONTENT OF TUMOURS

Case	Tumour (weight in g.)	Amine content (mg. per g. of wet wt.)	Ratio (noradrenaline/ adrenaline)
3	50	1·6	4·0
4	46	2·0	9·0
5	67	2·4	1·9
F	72	3·2	9·0
G	680	4·7	0·66

There seems to be no correlation between the size of the tumour and its amine content on the one hand and the clinical picture on the other. Case 4 had malignant hypertension with symptoms for five years, while Case 5 had mild symptoms for six months. The size of the tumours and their amine content were similar (Table IV). This may be accounted for by differences in the rate of tumour growth.

The rate of release of amine varies considerably from case to case, and not necessarily in relation to the tumour size and amine content. Case 3 had a urinary excretion 8 to 9 times greater than Case 4, but the tumour size and amine content were nearly the same (Table IV). This raises the question of which factors are important in controlling the release of amine from the tumour. It is not clear if a mechanical stimulus, like palpation or postural change, is directly effective or whether it initiates a nervous reflex. No account of the nerve supply to these tumours has been found. As mentioned above, palpation did not provoke an attack in any of our patients, but in Case 4 two typical attacks were induced by heating during the maximal heat elimination test. This was possibly a nervous reflex, though humoral factors are not excluded.

The relative proportion of amines in the tumours was similar to that in the urine as stated by Engel and Euler (1951). There was no extra-suprarenal tumour in the present series, yet the proportion of noradrenaline in the urine was very high in two of the cases (4 and F, Table III). This opposes the view of Euler (1951) that it is possible to presume an extra-suprarenal site in cases with a high percentage of noradrenaline excretion.

It is clear that the estimation of the urinary adrenaline and noradrenaline offers the best available special method of diagnosis. Certainly no false positive result has been obtained, but it may be premature to claim that no false negative has occurred.

OPERATION AND THE MANAGEMENT OF THE PATIENT

All the tumours were successfully removed by Mr. A. Dickson Wright under general anæsthesia given by Dr. L. H. Morris. In all our patients except one (Case 2) the blood pressure fell after removal of the tumour, and was restored to normal levels by intravenous infusions of noradrenaline or adrenaline in saline. Noradrenaline, which is a more effective pressor agent, was used in the three most recent cases, and it was necessary to infuse a large amount to maintain the pressure. The concentration varied from 10 to 20 mg. noradrenaline per litre of normal saline, and the rate was adjusted according to the effect on blood pressure. The infusion was first slowed and then stopped after 24 to 36 hours. Atropine was never used before operation in these patients as Barnett *et al.* (1950) have shown the increased rise in blood pressure which sometimes accompanies infusions of noradrenaline after administration of atropine.

Course and Prognosis

A feature of considerable interest in this series is the length of history; with this it is convenient also to consider the length of remissions (if any), and the prognosis. Case 1 had symptoms for 18 months; remissions did not exceed a week even in the early stages, and later were absent: with the advent of malignant hypertensive retinopathy and increasingly severe symptoms, the prognosis must have been extremely grave. In Case 2 there is no doubt that attacks had occurred for 8 years before operation, and it is at least possible that they began at about the age of 11 years, 20 years before operation. Remissions lasting several months occurred after 1941, but if his childhood symptoms represent the effects of this tumour, then there was freedom from symptoms for 10 years. Although this would indicate a benign course, he was rapidly deteriorating in health, with increasingly severe and frequent attacks and breathlessness. It is worth noting that his tumour was the largest in our observed cases, weighing 200 g. In Case 3, attacks had occurred for 2 years and were separated by intervals of a week or two at first; latterly her course was one of rapid deterioration, with frank left heart failure. In Case 4 the attacks had been of moderate severity for 5 years, with apparently remissions of not longer than a few days, even at the commencement; her downhill course into malignant hypertension was slow but continuous. Case 5 had the shortest history; the most direct questioning could not elicit symptoms for more than 6 months before operation, and he himself had not been disturbed by symptoms for more than 6 weeks; the attacks were, from the start, not more than a few days apart. Despite this short history, his tumour was the second largest.

All our patients, except Case 2, showed the profound fall in pressure at operation which is usually seen after removal of the tumour. In Case 1 it has risen again to a high level, but the retinal signs of malignant hypertension, which disappeared in the first three months after operation, have not returned; he has been at full-time work for two years. Case 2 has a normal blood pressure, is symptom free and at work. In Case 3 the pressure is near to normal, and she is free from symptoms. Ten months after operation on Case 4, paroxysms have not returned, but the pressure has risen again to high levels; the fundi, however, show improvement, with hardening of the exudates and disappearance of the papillœdema. Case 5 has a normal bood pressure, and is at full-time work, with no symptoms. In three of our patients, therefore, the pressure has remained at or near normal since operation. In the other two, however, there has been a return to high levels of pressure within a few weeks. Both originally showed the retinal signs of malignant hypertension and these disappeared with operation in both and have not returned.

The reason for the persistent hypertension in these two patients after excision of the tumours is unknown. The hypertension was not due to secretion from a second phæochromocytoma as shown by the normal values found for the urinary pressor amines and the return to normal of the maximal heat elimination from the hand. It is possible that both were cases of co-called essential hypertension and that the phæochromocytoma was superimposed. Evidence of an inherited disposition to hypertension was not convincing. The only sister of Case 1 had died from hypertension in childbirth, aged 20, at which age severe essential hypertension is very rare; the pressures of his parents were unknown and his brother, aged 42, had a normal pressure. The mother of Case 4, aged 69, had a blood pressure of 170/105; that of the father, who died of pneumonia, was unknown. The incidence of diastolic pressures of 120 mm. Hg or above, between the ages of 40 and 49 in a random sample of the general population, has been found to be 1·2 per cent in both men and women (personal observation, M.H. and G.S.C.S.). Thus it is extremely unlikely that two out of five cases would have shown pressures of this order if the previous existence of a phæochromocytoma were not significant. Moreover, the only other case observed in this hospital and reported by Barnet *et al.* (1950) also showed persistent hypertension after excision of a phæochromocytoma. We are thus led to the conclusion that the residual hypertension was in some way a consequence of the tumour. This conclusion, which must be provisional, is in line with other experience that hypertension may persist after what may be regarded as its primary cause has been removed.

Thus Pickering and Heptinstall (1953) reported seven cases of presumed unilateral pyelonephritis, three of which experienced no fall of pressure after excision of the diseased kidney, and all of which showed some residual hypertension.

SUMMARY

Five cases of phæochromocytoma are reported and their clinical features discussed.

Special diagnostic procedures are considered—of these the maximal heat elimination is simple and useful. Pharmacological tests with piperoxane, regitin, and histamine are discussed.

The estimation of urinary adrenaline and noradrenaline is confirmed as the best available special method of diagnosis.

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